REMARKS

Claims 1-15 and 17-26 are pending. Claims 3-9 and 19-26 are withdrawn from consideration. Claims 1, 2, 10-15, and 17-18 are under examination. In the present amendment, Applicants amend claims 1-2, 10-13, and 17-18 to recite "at least one archaeal polymerase and/or at least one archaeal polymerase fragment having polymerase activity." That amendment is supported in the specification, for example, at page 10, line 6, through page 11, line 2. No new matter is added by the present amendment.

Applicants have also replaced Figures 1 to 4 as originally filed on August 25, 2000, with the enclosed copies of Figures 1 to 4. The replacement drawings are of improved quality and add no new matter.

I. Rejection of Claims 1, 2, 10-15, 17, and 18 Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 1, 2, 10-15, 17, and 18 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.[1] Final Action at page 2. Specifically, the Examiner stated that:

> The specification as filed, is enabled for a DNA polymerase from *Pyrococcus furiosis*, but is not enabled for a DNA polymerase from any and all "samples".
>
> The art of biotechnology is a highly unpredictable art and it would be an undue burden for one of ordinary skill in the art to test any and all sources to see if they contained the claimed enzyme.

Id. at page 3. Applicants respectfully traverse.

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[1] The Examiner actually rejected claims 1, 2, 10-*16*, 17, and 18. Final Office Action at page 2. Presumably, the Examiner intended to reject claims 1, 2, 10-*15*, 17, and 18, because claim 16 was canceled in the Amendment and Response filed October 16, 2003.

In an interview with the undersigned on June 30, 2004, the Examiner further explained the basis for this rejection. Specifically, the Examiner stated that the specification enables obtaining archaeal polymerase from *Pyrococcus furiosus*, but it allegedly does not enable obtaining archaeal polymerase from any sample comprising archaeal polymerase. *See* Applicant Statement of Interview Summary, filed July 15, 2004, at page 1. The undersigned explained why the level of predictability in the art and the Examples in the specification enable the scope of the claims by reiterating arguments already of record. *See id.* at pages 1-2 (referring to Amendment and Response filed October 16, 2003, at pages 6-8, which is incorporated herein by reference). The Examiner stated during that interview that he would reconsider withdrawing the enablement rejection in view of those arguments. *See* Applicant Statement of Interview Summary at page 2. Those arguments are now reiterated below.

The specification provides guidance for "obtaining at least one substantially pure archaeal polymerase and/or archaeal polymerase fragment" from any sample comprising the same. For example, the specification provides examples of archaebacteria from which archaeal polymerase or a fragment thereof may be obtained. *See* specification at page 10, lines 9-11. The specification also contemplates "recombinantly produced archaeal polymerases that are purified by the novel methods of the invention." *Id.* at page 10, lines 18-19. The specification further states that "[t]he skilled artisan will appreciate that a variety of starting materials may be employed . . . . For example, supernatant fluid from cells that include vectors for expressing secreted forms of polymerase may be employed." *Id.* at page 15, lines 5-7. The specification

further provides detailed examples describing the isolation of archaeal polymerase from *Pyrococcus furiosus*. *Id.* at page 16, line 10, through page 20, line 17.

Furthermore, the guidance provided by the specification, together with the level of knowledge and predictability in the art, would have enabled one skilled in the art to use the claimed methods to obtain archaeal polymerase and/or a fragment thereof from any sample comprising the same. The MPEP states that:

> The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art . . . . The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification.

MPEP § 2164.03 at 2100-188 (8th ed. rev. 2, May 2004).

The specification describes the isolation of archaeal polymerase from *Pyrococcus furiosus* in Examples 1-3. If one uses a source other than *Pyrococcus*, then one might modify the specific details of the procedures used in Examples 1-3. However, such modification could be determined without undue experimentation by one skilled in the art having knowledge of routine protein purification methods. Such methods are described, for example, in Ausubel, F.M., et al., Current Protocols in Molecular Biology at pages 10.0.10-10.0.14, Figures 10.0.01–10.0.04 (Supplement 44, 1998), enclosed with the Amendment and Response filed October 16, 2003. Indeed, Ausubel discusses methods of protein purification from a variety of sources expressing either natural or recombinant proteins. *Id.* Thus, the specification, as well as the level of knowledge and predictability in the art, would have enabled the full scope of the claims.

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 2, 10-15, 17, and 18 under 35 U.S.C. § 112, first paragraph.

II. Rejection of Claims 1, 2, 10-15, 17, and 18 Under 35 U.S.C. § 103(a)

The Examiner rejected claims 1, 2, 10-15, 17, and 18 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bezuglyi, Bernard, or Grandgenett. Final Action at page 4. Applicants respectfully traverse this rejection. Applicants submit that the Examiner has failed to establish a prima facie case of obviousness for the reasons set forth in the Amendment and Response filed April 12, 2004, which the Examiner did not enter. Applicants now repeat the arguments in that Amendment and Response in Section A, below. Applicants also submit that art taught away from the claimed methods for the reasons set forth in Section B, below.

A. The Examiner Has Not Established a Prima Facie Case of Obviousness

To establish a *prima facie* case of obviousness, the cited documents must have suggested all the claim elements. MPEP § 2143 at 2100-129. None of the cited documents, either singly or in combination, would have suggested obtaining an archaeal polymerase and/or archaeal polymerase fragment. Therefore, the cited documents would have failed to render the claims obvious.

Furthermore, the Examiner appears to argue that it would have been obvious to modify the cited documents to include archaeal cells and archaeal polymerases. Specifically, the Examiner alleged that:

> The references each teach a DNA polymerase being purified using PolyU Sepharose chromatography.
>
> It would have been obvious to use the specific types of [archaeal] polymerases and cells since such cells and enzymes are well known in the art.

> To use such enzymes and cells are simply the choice of the artisan in an effort to optimize the desired results.

Final Action at page 4.

To modify the cited documents, the Examiner must provide some motivation or suggestion to do so. See MPEP § 2143.01 at 2100-129 – 2100-130. The Examiner has failed to meet this burden. In fact, it is the Applicants' own disclosure that provides such a suggestion or motivation. *See, e.g.*, specification at page 4, lines 6-14, disclosing a motivation to obtain highly purified archaeal polymerase, so that PCR can be optimized through the controlled addition of accessory factors. The Examiner may not rely on the Applicant's own disclosure to supply the necessary motivation. M.P.E.P. § 2143 at 2100-129.

The Examiner further stated that, "[t]o use such archaebacterial DNA polymerases is known in the art as is shown by applicant's own admission of the art as shown by Lasken et al. on page 2 of the applicant's specifcation." Final Action at page 4. Lasken observed that PCR reactions using archaeal polymerases were inhibited in the presence of dUrd-containing oligonucleotides, whereas PCR reactions using non-archaeal polymerases were not inhibited in the presence of dUrd-containing oligonucleotides. Specification, paragraph bridging pages 2-3. The fact that certain archaeal polymerases may have been known in the art and used in PCR reactions would not have rendered the claims obvious, because such polymerases and uses are not what is claimed. The claims encompass a method of obtaining at least one archaeal polymerase and/or at least one archaeal polymerase fragment. Thus, Lasken would have failed to cure the deficiencies of Bezuglyi, Bernard, or Grandgenett.

Furthermore, Bezuglyi, Bernard, or Grandgenett, in view of Lasken's observations, would not have suggested the desirability of purifying archaeal polymerases and/or fragments thereof using the claimed methods. See MPEP § 2143.01 at 2100-129 ("The prior art must suggest the desirability of the claimed invention."). As discussed above, it is the Applicants' own specification that suggests obtaining substantially pure archaeal polymerase, so that PCR can be optimized through the controlled addition of accessory factors. In contrast, the mere allegation that the method of Bezuglyi, Bernard, or Grandgenett *could have been* used to purify known archaeal polymerases does not render the claims obvious. See MPEP § 2143.01 at 2100-131 (citing *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990) ("The mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination.") (emphasis in original).

Accordingly, the Examiner has failed to establish prima facie obviousness of claims 1, 2, 10-15, 17, and 18.

B. Art Taught Away from the Claimed Methods

The claims are directed to methods for obtaining ". . . at least one archaeal polymerase and/or at least one archaeal polymerase fragment having polymerase activity using Poly U Sepharose chromatography . . . . " Archaeal polymerases and/or fragments thereof having polymerase activity are DNA-dependent DNA polymerases (i.e., they use DNA as a template). Applicants assert that art taught away from using Poly U Sepharose to obtain DNA-dependent DNA polymerases, such as archaeal polymerases and/or fragments thereof. See MPEP § 2141.02 at 2100-127 ("Prior art

must be considered in its entirety, including disclosures that teach away from the claims.")

The MPEP states that "the totality of the prior art must be considered, and *proceeding contrary to accepted wisdom in the art is evidence of nonobviousness.*" MPEP § 2145 Part X.D.3 at 2100-162 (emphasis added) (citing *In re Hedges,* 228 USPQ 685, 687 (Fed. Cir. 1986)). In *Hedges*, Applicant's claimed process for sulfonating diphenyl sulfone at high temperature was contrary to accepted wisdom because the prior art *as a whole* suggested using lower temperatures for optimum results. *Id.* at 686-87.

Here, use of Poly U Sepharose to purify archaeal polymerase and/or a fragment thereof would have been contrary to teachings that taught away from the use of Poly U Sepharose for the purification of DNA-dependent DNA polymerases. For example, the 1998 "Biodirectory" from Amersham Pharmacia Biotech recommended Poly(U) Sepharose 4B for purifying reverse transcriptase, which is an *RNA*-dependent DNA polymerase. (*See* Amersham Pharmacia Biotech 1998 Biodirectory at page 221, submitted in an Information Disclosure Statement filed January 5, 2001, a copy of which is enclosed for the Examiner's convenience.) However, the Biodirectory recommended different chromatographic media, i.e., DNA-agarose and DNA-cellulose, for purifying *DNA*-dependent DNA polymerases. Coming from Amersham Pharmacia Biotech, an internationally known supplier of chromatographic media, that recommendation would appear to represent accepted wisdom in the art of DNA polymerase purification. It is also consistent with the general notion that reverse transcriptase binds RNA, which contains uracil, whereas DNA-dependent DNA polymerases bind DNA, which does not

contain uracil. Thus, the claimed methods, which comprise using Poly U Sepharose chromatography to obtain archaeal polymerase (a *DNA*-dependent DNA polymerase) and/or a fragment thereof having polymerase activity, would have been contrary to these negative teachings.

The documents cited by the Examiner do not show otherwise. Grandgenett discusses purification of a *retroviral* (RNA-dependent) polymerase fragment using Poly U Sepharose. Thus, the method of Grandgenett does not suggest using Poly U Sepharose to obtain DNA-dependent DNA polymerases. Although Bezuglyi and Bernard purport to show methods of purifying DNA-dependent DNA polymerases using Poly U Sepharose, certain documents published after the publication of Bernard in 1991 and Bezuglyi in 1992 teach away from those methods, discussing the use of DNA-cellulose, and not Poly U Sepharose, for purifying DNA-dependent DNA polymerases. (*See, e.g.*, the enclosed publications by Shimizu et al. (1993) J. Biol. Chem. 268:27148-27153 at 27149 col. 2; Meißner et al. (1993) Nucleic Acids Res. 21:4893-4899 at 4894 col. 2; Aoyagi et al. (1994) J. Biol. Chem. 169:6045-6050, at 6046 col. 1; and Zhou et al. (1996) J. Biol. Chem. 271:29740-29745 at 29741 col. 2, as well as the Amersham Pharmacia Biotech 1998 Biodirectory.) Thus, Bernard and Bezuglyi did not reflect accepted wisdom, either at the time of or after their publication. Accordingly, one skilled in the art would not have been motivated to modify the teachings of Bernard and Bezuglyi to include archaeal polymerases and fragments thereof having polymerase activity.

Therefore, when the totality of the art of record is considered as a whole, it is evident that the claimed methods would have proceeded contrary to teachings that

taught away from the use of Poly U Sepharose for the purification of DNA-dependent DNA polymerases. *See In re Hedges*, 228 USPQ at 687 (Upon consideration of the prior art as a whole, the court found that "[o]n balance, Hedges proceeded contrary to the accepted wisdom. This is 'strong evidence of unobviousness.'"). Thus, the claimed methods are nonobvious.

Accordingly, the Examiner has failed to establish obviousness of claims 1, 2, 10-15, 17, and 18. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

CONCLUSION

Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the application. In the event that the Examiner does not find the application allowable, Applicants request that the Examiner contact the undersigned at (650) 849-6778 to set up an interview.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: November 5, 2004

By: Danielle Pasqualone
Danielle M. Pasqualone
Reg. No. 43,847

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P.D. 1998 P. 221 (1)

	Description	Ligand Substitution	Applications	Page
Immobilized DNA Media				
DNA-Agarose (denatured) single stranded	4% agarose matrix co-polymerized with ligand	1-3 mg denatured calf thymus DNA/ml gel	DNA polymerase, RNA polymerase, T4 polynucleotide kinase, exonuclease, other deoxy-ribonucleases	222
DNA-Cellulose (native DNA) double stranded	cellulose	0.25-1.5 mg native calf thymus DNA/ml gel	Glucocorticoid receptor, DNA polymerase, DNA binding proteins, exonuclease	222
DNA-Cellulose (denatured)	cellulose	0.25-1.5 mg denatured calf thymus DNA/ml gel	RNA polymerase, DNA polymerase, DNA binding proteins, DNases, exonucleases	222
Immobilized Nucleotide Media				
2'5' ADP Sepharose 4B	NADP analogue; 0.4 mg glucose-6-phosphate dehydrogenase/ml gel	2 µmol ligand/ml gel	NADP-dependent dehydrogenases	222
5' AMP Sepharose 4B	NAD analogue; 10 mg lactate dehydrogenase/ml gel	2 µmol ligand/ml gel	NAD-dependent dehydrogenases, ATP-dependent kinases	222
7-Methyl-GTP Sepharose 4B	Sepharose 4B matrix	0.2 µmol ligand/ml gel	Eukaryotic mRNA Cap-Binding Protein	222
Polynucleotide Media				
Poly(A) Sepharose 4B	Polyadenylic acid coupled via N6-amino groups. Results in multi-point covalent attachment of chains ≈100 nucleotides long.	Contains ≈ 0.25 mg ligand/ml gel. Binds > 0.5 mg poly(U) per ml gel. Antibodies to nucleic acids and tubulin assembly protein	mRNA-binding proteins, poly(A)-binding RNA, viral RNA, DNA-dependent RNA polymerase, antibodies	222
Poly(U) Sepharose 4B	Polyuridylic acid chains coupled via the tautomeric enolate form of the nucleotides. Results in multi-point attachment of chains ≈100 nucleotides long.	Contains ≈ 0.5 mg ligand/ml gel. Binds ≈ 150 µg mRNA (equiv. to ≈ 5 AU) per ml gel	mRNA, reverse transcriptase, interferon and nucleic acids from plants	222
AGPoly(I)•Poly(C) Type 6* Agarose-Polyribonosinic Acid •Polyribocytidylic Acid	Sepharose 4B matrix	1-4 mg ligand/ml gel	Interferon induction	222
AGPoly(U) Type 6 Agarose-Polyribouridylic Acid	Sepharose 4B matrix	1-4 mg ligand/ml gel	Detection of nucleotide sequences, isolation of ribosomes, mRNA and polynucleotide 5'-triphosphatase	222

* *The linkage is formed by reacting the ligand directly with cyanogen bromide-activated Sepharose.*

References

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3. Schweiger, A. and Mazur, G. Isolation and characterization of a soluble protein from Ehrlich ascites carcinoma cell cytoplasm with a high affinity for polyadenylate. *Hoppe-Seyler's Z. Physiol. Chem* 357, 481 (1976).
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REPLACEMENT DRAWINGS:

The attached three (3) sheets of drawings include Figures 1 to 4. These sheets replace the original sheets that include Figures 1 to 4.